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(54) Method of treating certain cancers using an estrogen agonist/antagonist

(57) The present invention provides methods of treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma using an estrogen agonist / antagonist. The present invention also provides kits that contain an estrogen agonist /antagonist for treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

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Description

Field of the Invention

[0001] The present invention provides methods of treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell caranoma that comprise administering to a patient having cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma a therapeutically effective amount of an estrogen agonist / antagonist. The present invention also provides kits for treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma that comprises a pharmaceutical composition comprising an estrogen agonist / antagonist and instructions for administering the pharmaceutical composition to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

Background of the Invention

[0002] Cancer is still one of the most dreaded diseases, and much effort and money has been spent trying to discover ways to treat cancer. The present invention provides methods of treating certain cancers, namely cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

[0003] There are two main types of cancer of the liver. The first type is the result of metastasis of cancer from another area in the body. In this type of liver cancer, a cancer cell from another part of the body migrates to the liver and begins growth and tumor formation there. Commonly, the cancer cells that metastasize to the liver come from cancer in the lungs, breast, colon, pancreas or stomach.

[0004] The second general type of liver cancer has been called primary liver cancer. This type is composed of subtypes of cancers such as hepatocelluar carcinoma, which is the most common type of liver cancer, fibrolamellar carcinoma, cholangiocarcinoma, hepatoblastoma and angiosarcoma.

[0005] Ovarvian cancer is the second most commonly diagnosed and most deadly gynecologic malignancy. Ovarian cancer affects predominantly perimenopausal and postmenopausal women.

[0006] Desmoid tumors, also called aggressive fibromatosis, are dense connective tissue tumors.

[0007] Glioma is a type of brain tumor, which accounts for 45% of intracranial tumors.

[0008] Pancreatic cancer has several varieties including ductal adenocarcinoma, cystadenocarcinoma, intraductal papillary-mucinous tumors, insulinoma, Zollinger-Ellison Syndrome (also known as gastrinoma), vipoma and glucagonoma.

[0009] Renal cell carcinoma accounts for about two percent of cancers.

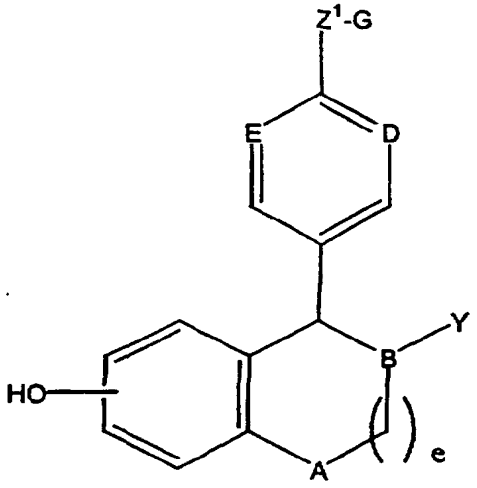
[0010] The cancers listed above can all be treated by administering to a patient suffering therefrom a therapeutically effective amount of an estrogen agonist /antagonist.

[0011] The use of tamoxifen to treat ovarian cancer, heptaocellular carcinoma, desmoid tumors, malignant gliomas, carcinoma of the pancreas and melanoma is discussed in Gelman, Edward P., *Tamoxifen for the Treatment of Malignancies Other Than Breast and Endometrial Carcinoma,* Seminars in Oncology, Vol. 24, No. 1, Suppl I (February), 1997, pp SI-65-SI 70.

Summary of the Invention

[0012] The present invention provides methods of treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma, the methods comprising the step of administering to a patient having cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma a therapeutically effective amount of an estrogen agonist / antagonist.

[0013] In a preferred embodiment of the methods, the estrogen agonist / antagonist is a compound of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;
B, D and E are independently selected from CH and N;
Y is

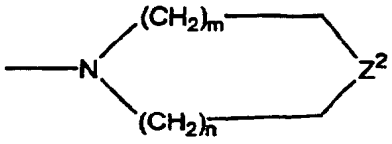
(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;
(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;
(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;
(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;
(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;
(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4; or
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

Z^1 is

(a) $-(CH_2)_p W(CH_2)_q-$;
(b) $-O(CH_2)_p CR^5R^6-$;
(c) $-O(CH_2)_pW(CH_2)_q-$;
(d) $-OCHR^2CHR^3-$; or
(e) $-SCHR^2CHR^3-$;

G is

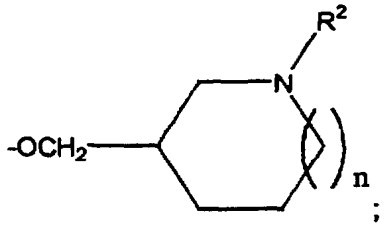
(a) $-NR^7R^8$;
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

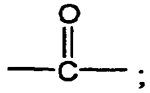
Z^1 and G in combination may be



;

W is

(a) $-CH_2-$;
(b) -CH=CH-;
(c) -O-;
(d) $-NR^2-$;
(e) $-S(O)_n-$;
(f)



;

(g) $-CR^2(OH)-$;
(h) $-CONR^2-$;
(i) $-NR^2CO-$;
(j)

;

or
(k) -C≡C-,

R is hydrogen or C_1-C_6 alkyl;
R^2 and R^3 are independently

(a) hydrogen; or
(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;

(b) halogen;
(c) C_1-C_6 alkyl;
(d) C_1-C_4 alkoxy;
(e) C_1-C_4 acyloxy;
(f) C_1-C_4 alkylthio;
(g) C_1-C_4 alkylsulfinyl;
(h) C_1-C_4 alkylsulfonyl;
(i) hydroxy (C_1-C_4)alkyl;
(j) aryl (C_1-C_4)alkyl;
(k) $-CO_2H$;
(l) -CN;
(m) -CONHOR;
(n) $-SO_2NHR$;
(o) $-NH_2$;
(p) C_1-C_4 alkylamino;
(q) C_1-C_4 dialkylamino;
(r) $-NHSO_2R$;
(s) $-NO_2$;
(t) -aryl; or
(u) -OH;

R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;
R^7 and R^8 are independently

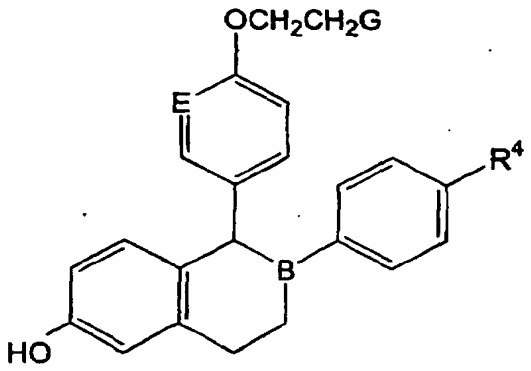
(a) phenyl;
(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;
(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
(d) H;
(e) C_1-C_6 alkyl; or
(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
e is 0, 1 or 2;
m is 1, 2 or 3;
n is 0, 1 or 2;
p is 0, 1, 2 or 3;
q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

[0014] In another preferred embodiment of the methods, the estrogen agonist /antagonist is a compound of formula (IA)



(IA)

wherein G is

;

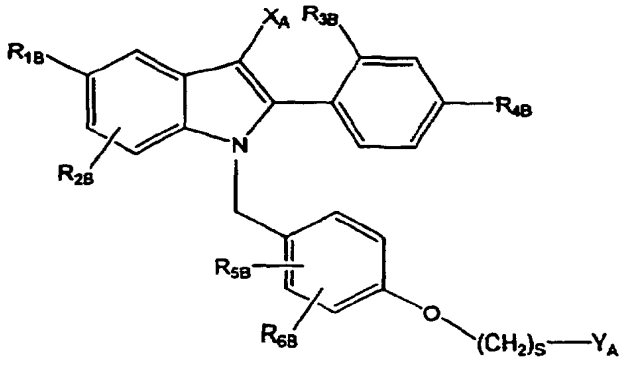
[0015] R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

[0016] In another preferred embodiment of the methods, the estrogen agonist /antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt. or a prodrug thereof.

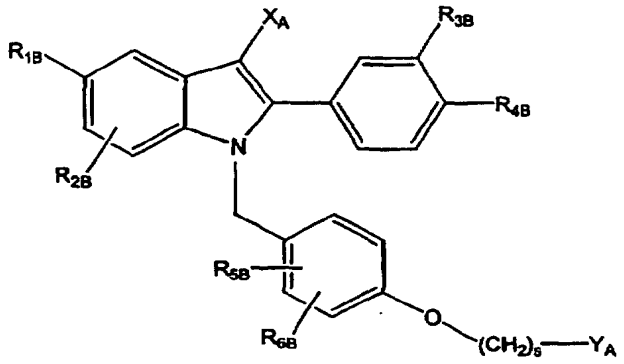
[0017] In another preferred embodiment of the methods, the estrogen agonist /antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

[0018] In another preferred embodiment of the methods, the estrogen agonist /antagonist is 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, raloxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b] thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, or an optical or geometric isomer thereof; pharmaceutically acceptable salt, N-oxide, ester, quatemary ammonium salt, or prodrug thereof.

[0019] In another preferred embodiment of the methods, the estrogen agonist /antagonist is a compound of formula V or VI:



(V)



(VI)

wherein:

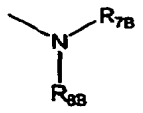
R_{1B} is selected from H, OH, -O-C(O)-C_1-C_{12} alkyl (straight chain or branched), -O-C_1-C_{12} alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH, -O-C(O)-C_1-C_{12} (straight chain or branched), -O-C_1-C_{12} (straight chain or branched or cyclic). halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is the moiety:



wherein:

a) R_{7B} and R_{8B} are independently selected from the group of H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, -CF_3, or -OCF_3; or

b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

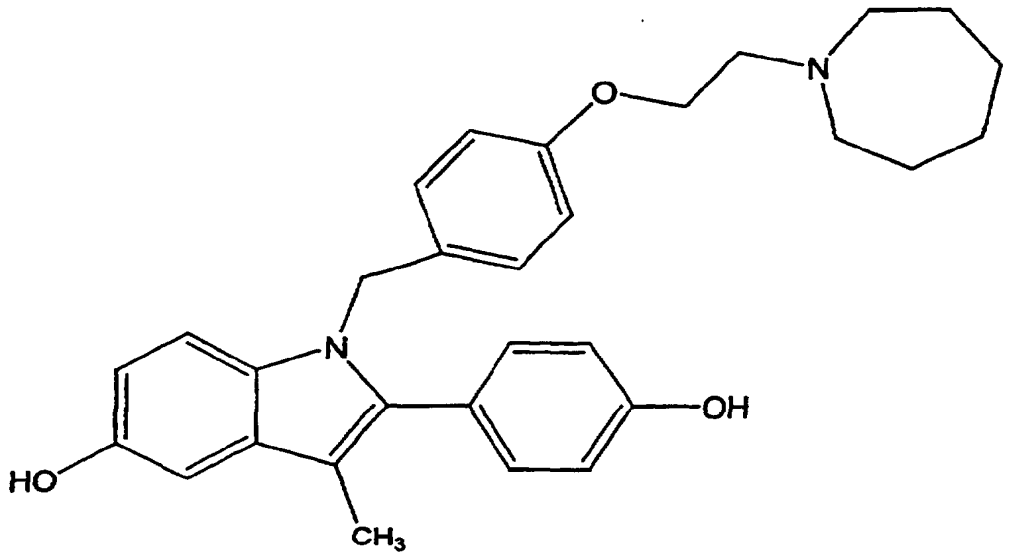
c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocyde containing one nitrogen heteroatom, the heterocyde being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen. hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl. C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2$ R_{1B}, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy. C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2 H, -CN, -$CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl, or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

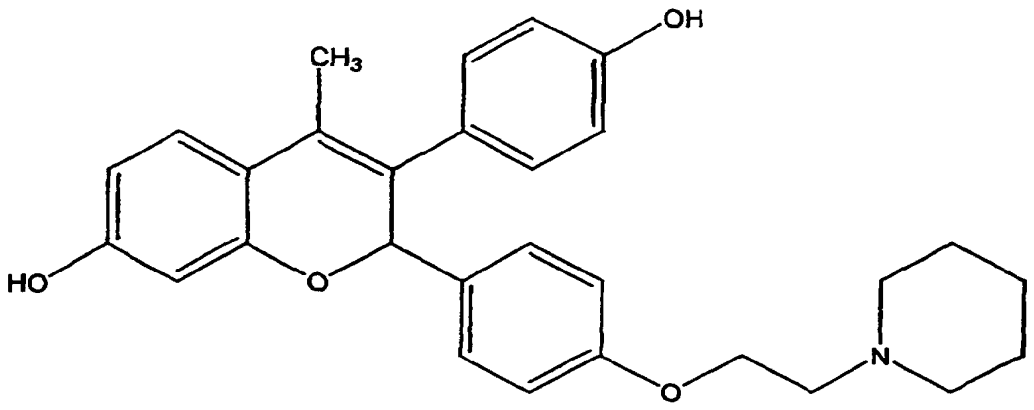
[0020] In another preferred embodiment of the methods, the estrogen agonist/antagonist is the compound of formula Va:



(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quatemary ammonium salt or prodrug thereof.

[0021] In another preferred embodiment of the methods, the estrogen agonist/antagonist is the compound of formula III (EM-652) or formula IV (EM-800) below:



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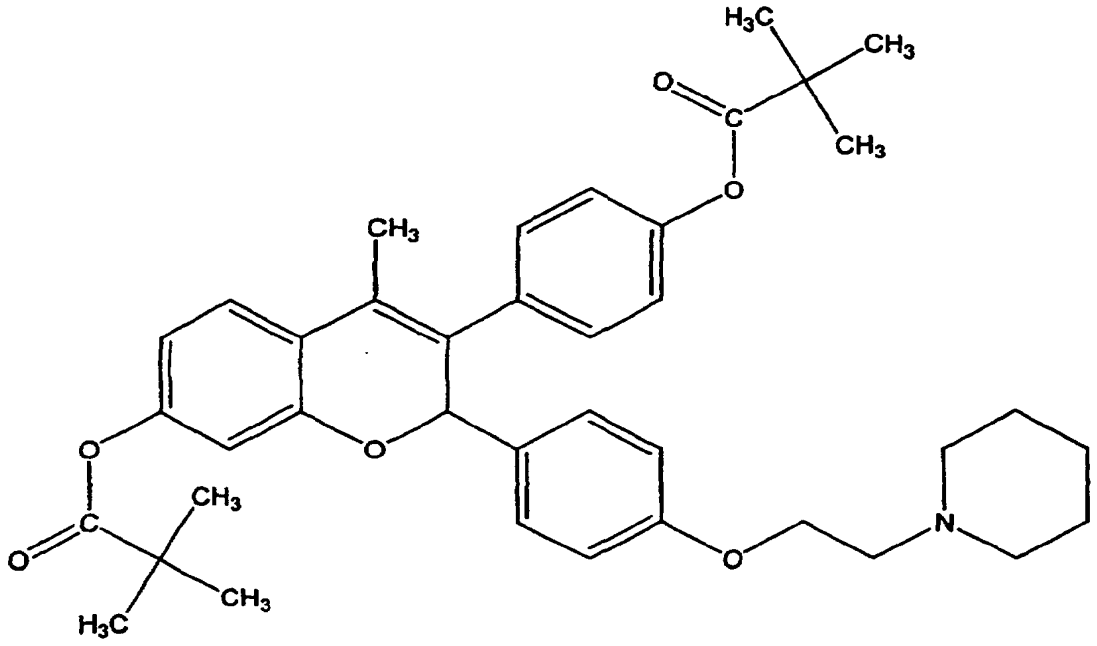


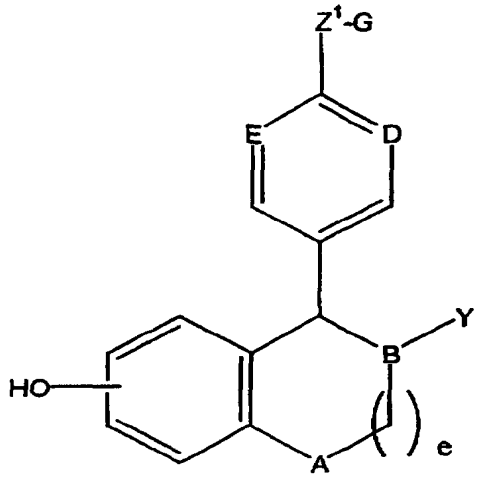
(IV)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

[0022] Also provided by the present invention are kits for use by a consumer to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma, the kits comprising:

(a) a pharmaceutical composition comprising an estrogen agonist / antagonist; and
(b) instructions describing a method of using the pharmaceutical composition to treat cancer of the liver, ovarian cancer. a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

[0023] In a preferred embodiment of the kits, the estrogen agonist / antagonist is a compound of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;
B, D and E are independently selected from CH and N;
Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;
(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;
(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;
(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;
(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;
(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4; or
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

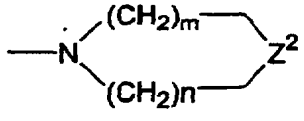
Z^1 is

(a) $-(CH_2)_pW(CH_2)_q-$;
(b) $-O(CH_2)_p\ CR^5R^6-$;
(c) $-O(CH_2)_pW(CH_2)_q-$;
(d) $-OCHR^2CHR^3-$; or
(e) $-SCHR^2CHR^3-$;

G is

(a) $-NR^7R^8$;

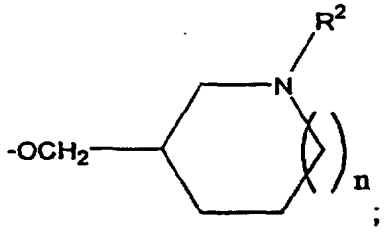
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O- -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

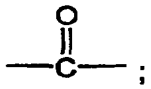
(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



W is

(a) $-CH_2-$;
(b) -CH=CH-;
(c) -O-;
(d) $-NR^2-$;
(e) $-S(O)_n-$;
(f)



(g) $-CR^2(OH)-$;
(h) $-CONR^2-$;
(i) $-NR^2CO-$;
(j)

or
(k) -C≡C-;

R is hydrogen or C_1-C_6 alkyl;
R^2 and R^3 are independently

(a) hydrogen; or
(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;
(b) halogen;

(c) C_1-C_6 alkyl;
(d) C_1-C_4 alkoxy;
(e) C_1-C_4 acyloxy:
(f) C_1-C_4 alkylthio;
(g) C_1-C_4 alkylsulfinyl;
(h) C_1-C_4 alkylsulfonyl;
(i) hydroxy (C_1-C_4)alkyl;
(j) aryl (C_1-C_4)alkyl;
(k) -CO_2H;
(l) -CN;
(m) -CONHOR;
(n) -SO_2NHR;
(o) -NH_2;
(p) C_1-C_4 alkylamino;
(q) C_1-C_4 dialkylamino;
(r) -$NHSO_2$R;
(s) -NO_2;
(t) -aryl; or
(u) -OH;

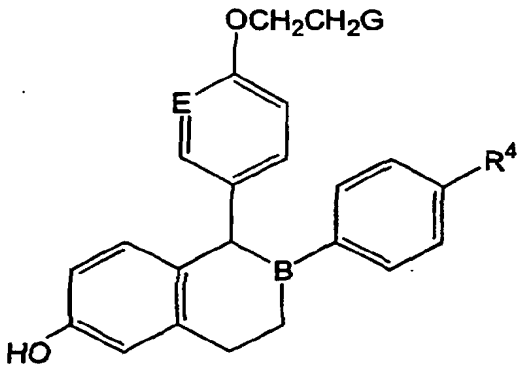
R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring,
R^7 and R^8 are independently

(a) phenyl;
(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;
(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
(d) H;
(e) C_1-C_6 alkyl; or
(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
e is 0, 1 or 2;
m is 1 , 2 or 3;
n is 0, 1 or 2;
p is 0, 1, 2 or 3;
q is 0, 1, 2 or 3;
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

[0024] In another preferred embodiment of the kits, the estrogen agonist /antagonist is a compound of formula (IA):



(IA)

wherein G is

;

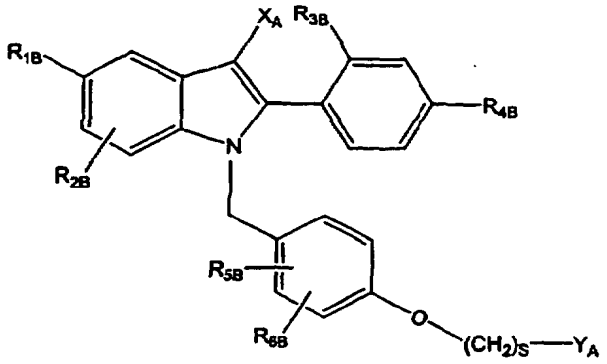
[0025] R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

[0026] In another preferred embodiment of the kits, the estrogen agonist /antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

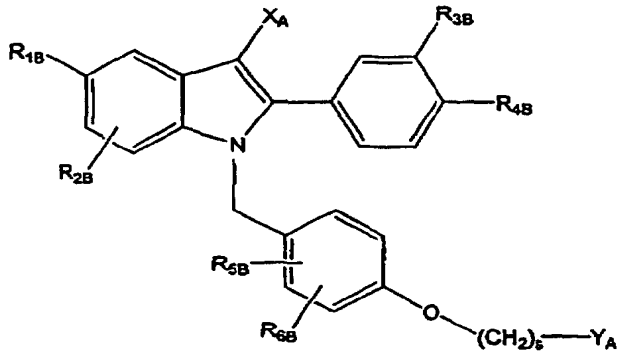
[0027] In another preferred embodiment of the kits, the estrogen agonist /antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

[0028] In another preferred embodiment of the kits, the estrogen agonist /antagonist is 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, raloxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-pheny}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b] thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, or an optical or geometric isomer thereof; pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug thereof.

[0029] In another preferred embodiment of the kits, the estrogen agonist / antagonist is a compound of formula V or VI:



(V)



(VI)

wherein:

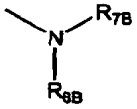
R_{1B} is selected from H, OH, -O-C(O)-C_1-C_{12} alkyl (straight chain or branched), -O-C_1-C_{12} alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH, -O-C(O)-C_1-C_{12} (straight chain or branched), -O-C_1-C_{12} (straight chain or branched or cyclic), halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is the moiety:



wherein:

a) R_{7B} and R_{8B} are independently selected from the group of H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, -CF_3, or -OCF_3; or

b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

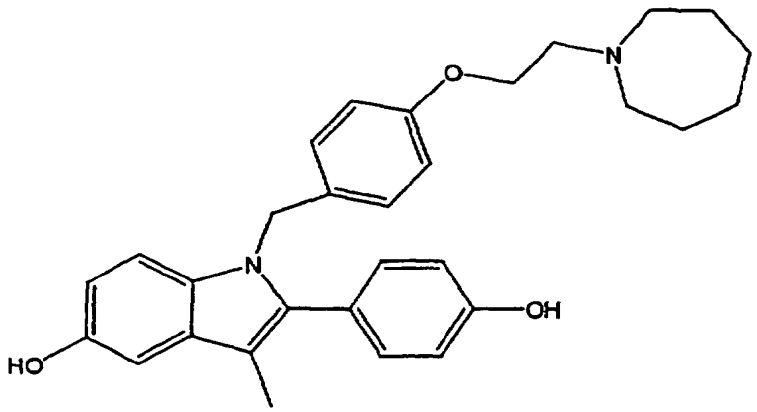
c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocyde containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy. C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocyde being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2 H, -CN, - $CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl, or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

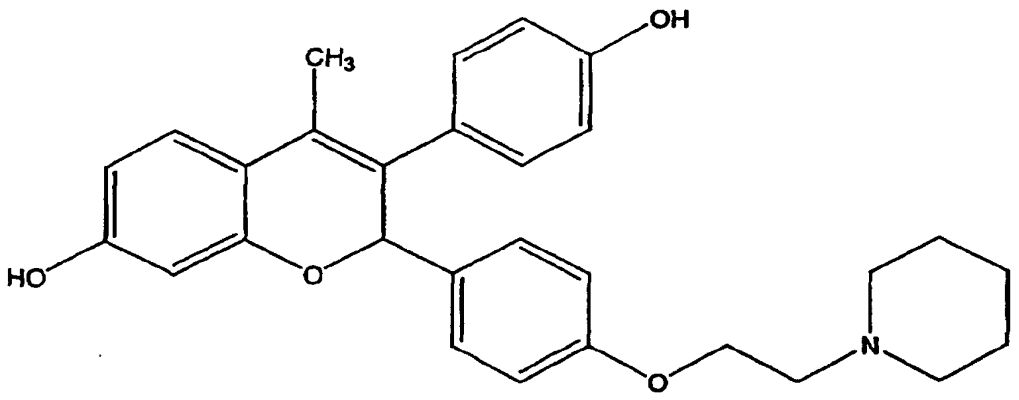
[0030] In another preferred embodiment of the kits, the estrogen agonist /antagonist is the compound of formula Va (TSE-424) below:



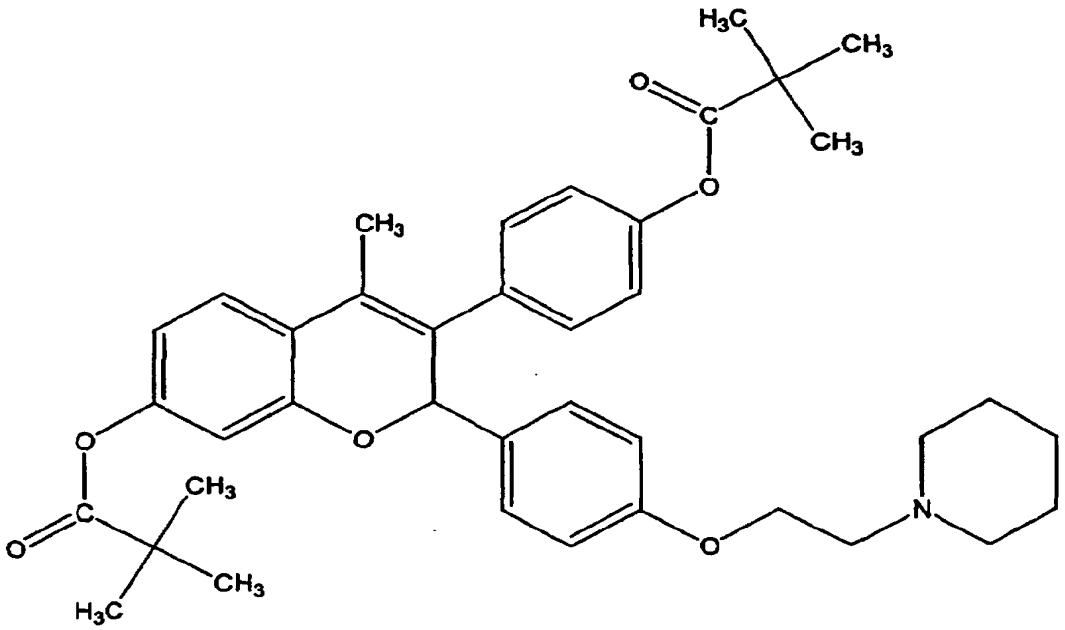
(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

[0031] In another preferred embodiment of the kits, the estrogen agonist /antagonist is the compound of formula III (EM-652) or formula IV (EM-800) below:



(III)



(IV)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

[0032] In another preferred embodiment of the kits, the kits further comprise an additional compound that is useful to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

Detailed Description of the Invention

[0033] The present invention provides methods of treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma, the methods comprising the step of administering to a patient having cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma a therapeutically effective amount of an estrogen agonist /antagonist. Also provided are kits for the treatment of cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma, which kits comprise a pharma-

ceutical composition that contains an estrogen agonist /antagonist and instructions describing methods of using the pharmaceutical composition to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

[0034] The terms "treat", "treatment", and "treating" include preventative (e.g., prophylactic) and palliative treatment or the act of providing preventative or palliative treatment.

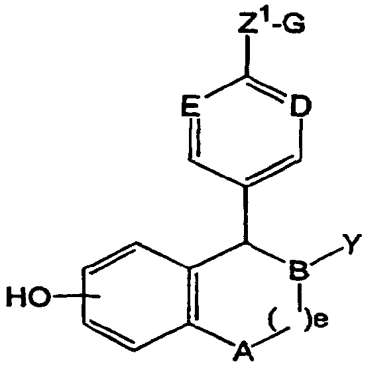
[0035] The term "patient" means animals, particularly mammals. Preferred patients are humans.

[0036] An "estrogen agonist / antagonist" is a compound that affects some of the same receptors that estrogen does, but not all, and in some instances, it antagonizes or blocks estrogen. It is also known as a "selective estrogen receptor modulator" (SERM). Estrogen agonists / antagonists may also be referred to as antiestrogens although they have some estrogenic activity at some estrogen receptors. Estrogen agonists / antagonists are therefore not what are commonly referred to as "pure antiestrogens". Antiestrogens that can also act as agonists are referred to as Type I antiestrogens. Type I antiestrogens activate the estrogen receptor to bind tightly in the nucleus for a prolonged time, but with impaired receptor replenishment (Clark, et al., Steroids 1973;22:707, Capony et al., Mol Cell Endocrinol, 1975;3:233).

[0037] "A therapeutically effective amount" is an amount of an estrogen agonist /antagonist that when administered to a patient having cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma provides for the treatment of one or more conditions or symptoms of the cancer. Preferably, tumor size is decreased upon administration of an estrogen agonist / antagonist.

[0038] The estrogen agonists / antagonists of the invention may be administered systemically or locally. For systemic use, the estrogen agonists / antagonists herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration can be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration can be performed at intervals ranging from weekly to once to three or more times daily.

[0039] Preferred estrogen agonists / antagonists of the present invention include the compounds described in U.S. Patent No. 5,552,412. Those compounds are described by the formula designated herein as formula (I) given below:



(I)

wherein:

A is selected from CH_2 and NR;
B, D and E are independently selected from CH and N;
Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4,
(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;
(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;
(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;
(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;
(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4; or
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

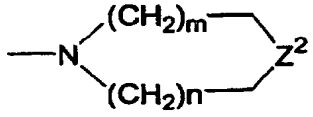
Z^1 is

(a) $-(CH_2)_p W(CH_2)_q-$;
(b) $-O(CH_2)_p CR^5R^6-$;
(c) $-O(CH_2)_pW(CH_2)_q-$;
(d) $-OCHR^2CHR^3-$; or
(e) $-SCHR^2CHR^3-$;

G is

(a) $-NR^7R^8$;

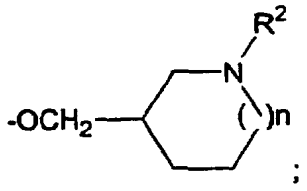
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

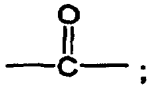
(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



W is

(a) $-CH_2-$;
(b) -CH=CH-;
(c) -O-;
(d) $-NR^2-$;
(e) $-S(O)_n-$;
(f)



(g) $-CR^2(OH)-$;
(h) $-CONR^2-$;
(i) $-NR^2CO-$;
(j)

;

or
(k) -C≡C-;

R is hydrogen or C_1-C_6 alkyl;
R^2 and R^3 are independently

(a) hydrogen; or
(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;
(b) halogen;
(c) C_1-C_6 alkyl;
(d) C_1-C_4 alkoxy;
(e) C_1-C_4 acyloxy;
(f) C_1-C_4 alkylthio;
(g) C_1-C_4 alkylsulfinyl;
(h) C_1-C_4 alkylsulfonyl;
(i) hydroxy (C_1-C_4)alkyl;
(j) aryl (C_1-C_4)alkyl;
(k) $-CO_2H$;
(l) -CN;
(m) -CONHOR;
(n) $-SO_2NHR$;
(o) $-NH_2$;
(p) C_1-C_4 alkylamino;
(q) C_1-C_4 dialkylamino;
(r) $-NHSO_2R$;
(s) $-NO_2$;
(t) -aryl; or
(u) -OH;

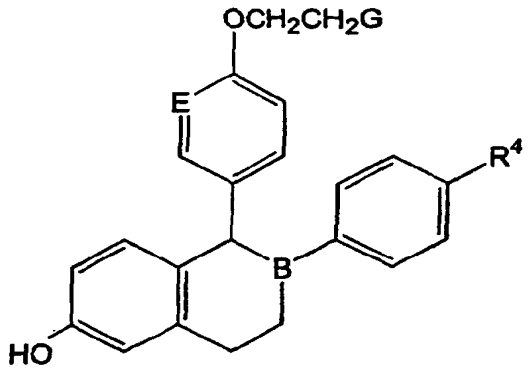
R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;
R^7 and R^8 are independently

(a) phenyl;
(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;
(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
(d) H;
(e) C_1-C_6 alkyl; or
(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;
a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
e is 0, 1 or 2;
m is 1 , 2 or 3;
n is 0, 1 or 2;
p is 0, 1, 2 or 3;
q is 0, 1, 2 or 3;

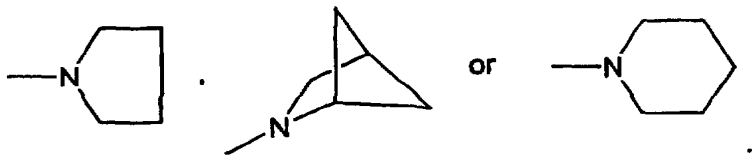
and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof.

[0040] Additional preferred compounds are disclosed in U.S. Patent No. 5,552.412 and are described by the formula designated herein as formula (IA):



(IA)

wherein G is



;

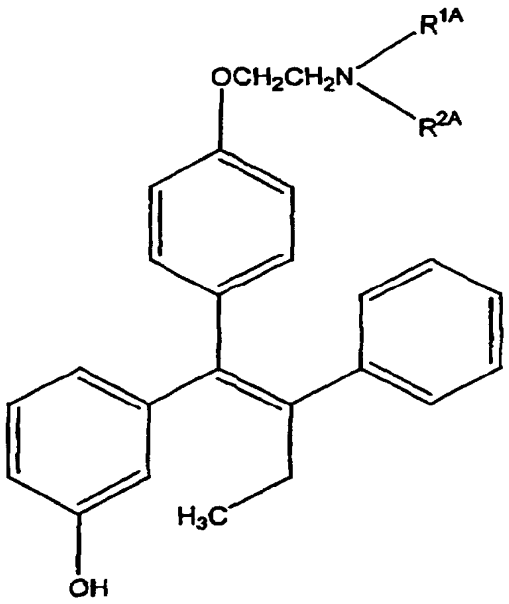
[0041] R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N, and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable add addition salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof.

[0042] Especially preferred compounds for the methods and kits of the invention are:

cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
(-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;
1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;
cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and pharmaceutically acceptable salts thereof.

[0043] An especially preferred salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol is the D-tartrate salt.

[0044] Other preferred estrogen agonists / antagonists are disclosed in U.S. Patent 5,047,431. The structure of these compounds are described by the formula designated herein as formula (II) below:



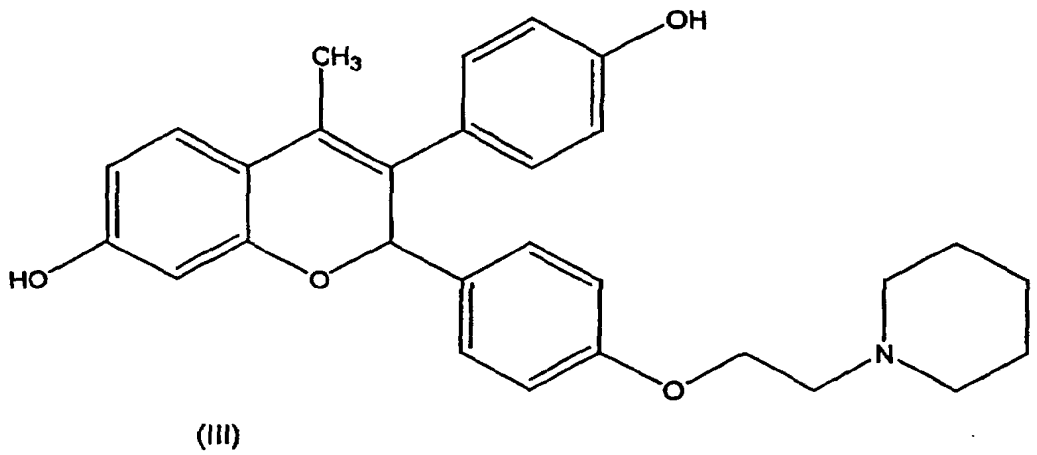
(II)

wherein

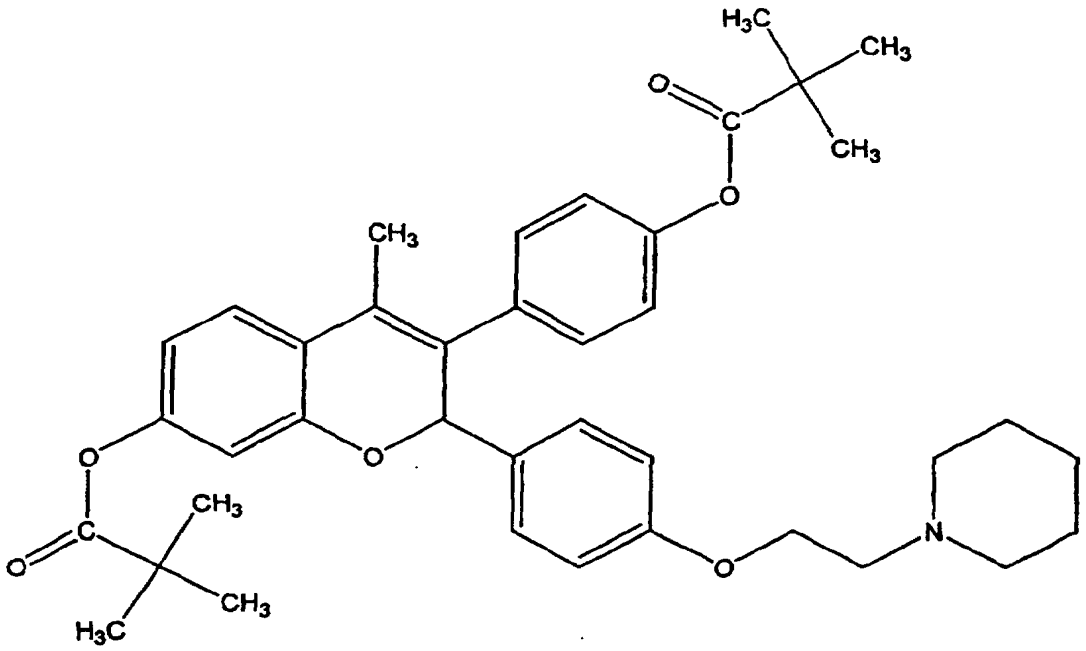
[0045] R^{1A} and R^{2A} may be the same or different and are either H, methyl, ethyl or a benzyl group; and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof. A preferred compound is droloxifene.

[0046] Additional preferred estrogen agonists / antagonists are the compounds disclosed in U.S. Patent No. 4,536,516; 4-hydroxy tamoxifen (i.e.. tamoxifen wherein the 2-phenyl moiety has a hydroxy group at the 4 position) and other compounds as disclosed in U.S. Patent No. 4,623,660; raloxifene: (methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-,hydrochloride) and other compounds as disclosed in U.S. Patent Numbers 4,418,068; 5,393,763; 5,457,117; 5,478,847 and 5,641,790; toremifene: (ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) and other compounds as disclosed in U.S. Patent Numbers 4,696,949 and 4,996,225; centchroman: 1-[2-[[4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy]-ethyl]-pyrrolidine and other compounds as disclosed in U.S. Patent No. 3,822,287; idoxifene: pyrrolidine, 1-[-[4-[[1-(4-iodophenyl)-2-phenyl-1-butenyl]phenoxy]ethyl] and other compounds as disclosed in U.S. Patent No. 4,839,155; 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol and other compounds as disclosed in U.S. Patent No. 5,484,795; and {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone and other compounds as disclosed in published international patent application WO 95/10513. Other preferred compounds include GW 5638 and GW 7604, the synthesis of which is described in Willson et al., J. Med. Chem., 1994;37:1550-1552.

[0047] Further preferred estrogen agonists / antagonists include EM-652 (as shown in the formula designated herein as formula (III) and EM-800 (as shown in the formula designated herein as formula (IV)). The synthesis of EM-652 and EM-800 and the activity of various enantiomers is described in Gauthier et al., J. Med. Chem.. 1997;40:2117-2122.

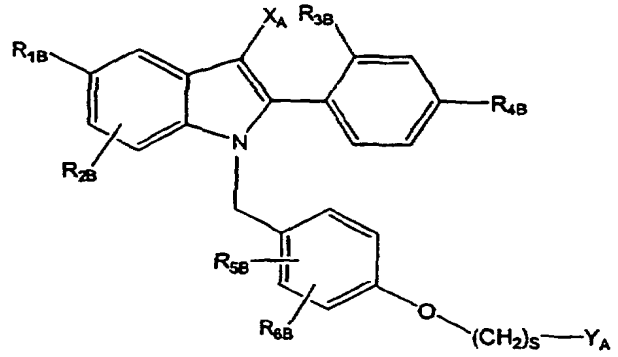


(III)

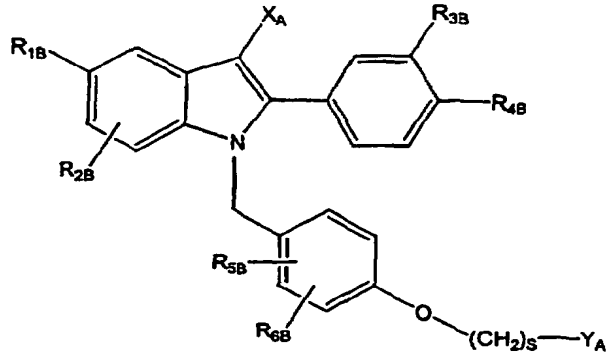


(IV)

[0048] Further preferred estrogen agonists / antagonists include TSE 424 and other compounds disclosed in U.S. Patent No. 5,998,402, U.S. Patent No. 5,985,910, U.S. Patent No. 5.780,497, U.S. Patent No. 5,880,137, and European Patent Application EP 0802183 A1 including the compounds described by the formulae designated herein as formulae V and VI, below:



(V)



(VI)

wherein:

R_{1B} is selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} (straight chain or branched or cyclic) alkyl ethers thereof, or halogens; or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

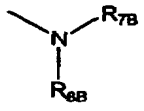
R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is selected from:

a) the moiety:



wherein R_{7B} and R_{8B} are independently selected from the group of H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, $-CF_3$, or $-OCF_3$;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heter-

oatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, -N=, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONHR_{1B}, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -NHSO_2R_{1B}, -NHCOR_{1B}, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, -N=, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONHR_1, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -NHSO_2R_{1B}, -NHCOR_{1B}, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, -N=, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONHR_{1B}, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -NHSO_2R_{1B}, -NHCOR_{1B}, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H-, -CN-, -CONHR_{1B}-, -NH_2, -N=, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -NHSO_2R_{1B}, -NHCOR_{1B}, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; and optical and geometric isomers thereof: and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

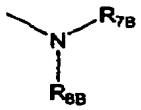
[0049] Preferred compounds of this invention are those having the general structures V or VI, above, wherein:

R_{1B} is selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, and halogen;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, halogen, cyano, C_1-C_6 alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R_{1B} is H, R_{2B} is not OH;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

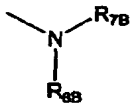
Y_A is the moiety:



R_{7B} and R_{8B} are selected independently from H, C_1-C_6 alkyl, or combined by -(CH_2)$_w$-, wherein w is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONH(C_1-C_4alkyl), -NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, -NHSO_2(C_1-C_4alkyl), -CO(C_1-C_4alkyl), and -NO_2; and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides esters, quaternary ammonium salts, and prodrugs thereof.

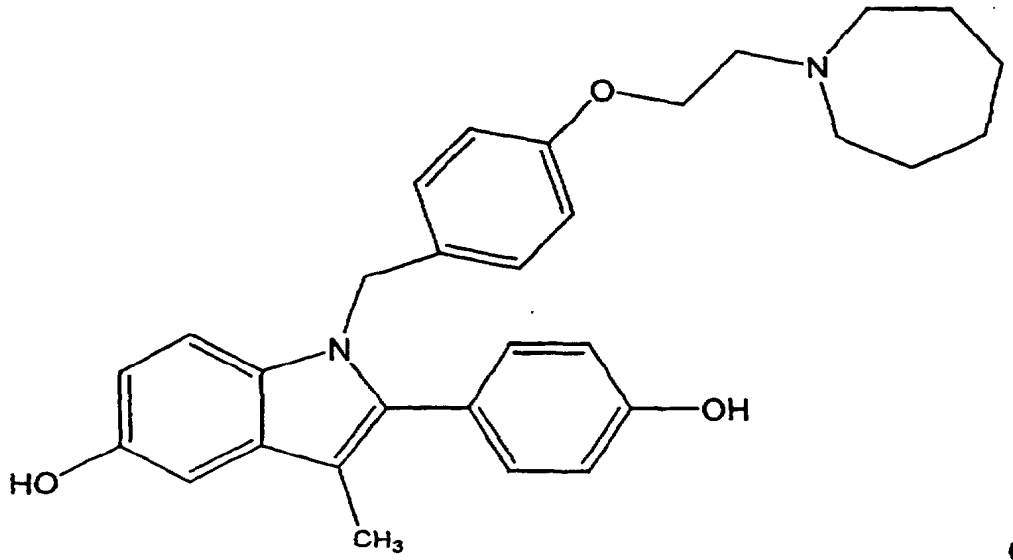
[0050] The rings formed by a concatenated R_{7B} and R_{8B}, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

[0051] Preferred compounds of structural formulas V and VI. above. are those wherein R_{1B} is OH; R_{2B} - R_{6B} are as defined above; X_A is selected from the group of Cl, NO_2, CN, CF_3, or CH_3; Y_A is the moiety



and R_{7B} and R_{8B} are concatenated together as $-(CH_2)_t-$, wherein t is an integer of from 4 to 6, to form a ring optionally substituted by up to three subsituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONH(C_1$-$C_4)$alkyl, $-NH_2$, C_1-C_4 alkylamino, $di(C_1$-$C_4)$alkylamino, $-NHSO_2(C_1$-$C_4)$alkyl, $-NHCO(C_1$-$C_4)$alkyl, and $-NO_2$; and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable add addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

[0052] Another preferred compound is TSE-424 as described by the formula designated herein as formula (Va) below:



(Va)

[0053] The estrogen agonists / antagonists of this invention can be administered in the form of pharmaceutically acceptable salts. The salts are conveniently formed, as is usual in organic chemistry, by reacting the compound, when basic, with a suitable add. The salts usually are quickly formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-forming add is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it. A preferred salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol is the D-(-)-tartrate salt. It will also be recognized that it is possible to administer amorphous forms of the estrogen agonists / antagonists.

[0054] The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically acceptable cationic salts" is intended to define, but is not limited to, such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth

metal salts (e g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine. piperazine. tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically acceptable add addition salts" is intended to define, but is not limited to, such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

[0055] One of ordinary skill in the art will recognize that certain estrogen agonists /antagonists of this invention will contain one or more atoms which may be in a particular stereochemical, tautomeric, or geometric configuration, giving rise to stereoisomers, tautomers and configurational isomers. All such tautomers and isomers and mixtures thereof are included in this invention. Hydrates and solvates of the compounds of this invention are also included.

[0056] The subject invention also includes isotopically-labeled estrogen agonists /antagonists, which are structurally identical to those disclosed above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds and of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0057] Those of ordinary skill in the art will recognize that physiologically active compounds which have accessible hydroxy groups can be administered in the form of pharmaceutically acceptable esters. The compounds of this invention can be effectively administered as an ester, formed on the hydroxy groups It is possible, as has long been known in pharmaceutical chemistry, to adjust the rate or duration of action of the compound by appropriate choices of ester groups.

[0058] Certain ester groups are preferred when a compound of this invention contains an ester. The estrogen agonists / antagonists including the compounds of formula I, IA, II, III, IV, V, Va, or VI may contain ester groups at various positions as defined herein above, where these groups are represented as -COOR, R is C_1-C_{14} alkyl, C_1-C_3 chloroalkyl, C_1-C_3 fluoroalkyl, C_5-C_7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro)methyl.

[0059] The dose of a compound of this invention to be administered to a subject is rather widely variable and subject to the judgement of the attending physician. It should be noted that it may be necessary to adjust the dose of a compound when it is administered in the form of a salt, such as a laureate, the salt forming moiety of which has an appreciable molecular weight. The particular dose of a compound administered according to this invention will be determined by the circumstances including, for example, the compound administered, the route of administration, and the severity of the condition being treated.

[0060] The following dosage amounts are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject. All doses set forth herein are daily doses of the free base form of the estrogen agonists /antagonists. Calculation of the dosage amount for other forms of the free base form such as salts or hydrates is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

[0061] The general range of effective administration rates of an estrogen agonist /antagonist is from about 0.001 mg/day to about 200 mg/day. A preferred rate range is from about 0.010 mg/day to about 100 mg/day. Of course, it is often practical to administer the daily dose of compound in portions, at various hours of the day. However, in any given case, the amount of compound administered will depend on such factors as the potency of the specific estrogen agonist/ antagonist, the solubility of the compound, the formulation used and the route of administration.

[0062] Methods of formulation are well known in the art and are disclosed, for example, in Remington: The Science and Practice of Pharmacy, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use within the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

[0063] Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the

mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[0064] Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[0065] A lubricant may be necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0066] Tablet disintegrators are substances that facilitate the disintegration of a tablet to release a compound when the tablet becomes wet. They include starches, clays, celluloses, algins and gums, more particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used as well as sodium lauryl sulfate.

[0067] Tablets are often coated with sugar as a flavorant and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established in the art.

[0068] When it is desired to administer a compound as a suppository, the typical bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

[0069] The effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The technique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film that resists dissolution for a predictable period of time. Topical formulations may be designed to yield delayed and/or prolonged percutaneous absorption of a compound. Even the parenteral preparations may be made long-acting, by dissolving or suspending the compound in oily or emulsified vehicles which allow it to disperse only slowly in the serum.

[0070] The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[0071] For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the add group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

[0072] Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0073] If a compound of the present invention comprises an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R^X-carbonyl, R^XO-carbonyl, $NR^XR^{X'}$-carbonyl where R^X and $R^{X'}$ are each independently (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, benzyl, or R^X-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, -C(OH)C(O)OY^X wherein Y^X is H, (C_1-C_6)alkyl or benzyl), -C(OY^{X0})Y^{X1} wherein Y^{X0} is (C_1-C_4) alkyl and Y^{X1} is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N, N-(C_1-C_6)alkylaminoalkyl, -C(Y^{X2}) Y^{X3} wherein Y^{X2} is H or methyl and Y^{X3} is mono-N- or di-N,N-(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[0074] Advantageously, the present invention also provides kits for use by a consumer to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma. The kits comprise a) a pharmaceutical composition comprising an estrogen agonist / antagonist; and b) instructions describing methods of using the pharmaceutical compositions to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

[0075] A "kit" as used in the instant application includes a container for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a resealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box.

[0076] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably, the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0077] It may be desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or other health care provider, or patient, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested or a card which contains the same type of information. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday," ... etc .... "Second Week, Monday, Tuesday, ..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

[0078] Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

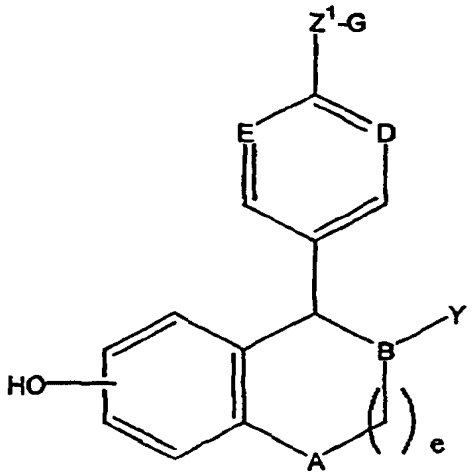
[0079] The kits of the present invention may also include, in addition to an estrogen agonist / antagonist, one or more additional pharmaceutically active compounds. Preferably, the additional compound is another estrogen agonist / antagonist or another compound useful to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma. The additional compound or compounds may be administered in the same dosage form as the estrogen agonist / antagonist or in different dosage forms. Likewise, the additional compounds can be administered at the same time as the estrogen agonist /antagonist or at different times.

[0080] Compounds that are used to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma and which can be used in combination with the estrogen agonists /antagonists of the present invention include 5-fluorouracil; cisplatin; paclitaxel; onconase; topotecan; hexamethylamine; ifsofamide; doxorubicin, etoposide, bleomycin; nitrosoureas such as carmustine, lomustine, procarbazine, semustine, and vincristine; methotrexate; carboplatin; actinomycin D, and streptozocin. The estrogen agonists / antagonists of the present invention can also be used in combination with radiation therapy.

[0081] All documents cited herein, including patents and patent applications, are hereby incorporated by reference.

Claims

1. The use of an estrogen agonist/antagonist of the formula (I)



(I)

wherein:

A is selected from CH_2 and NR;
B, D and E are independently selected from CH and N;
Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;
(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;
(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;
(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;
(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$. optionally substituted with 1-3 substituents independently selected from R^4;
(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4; or
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

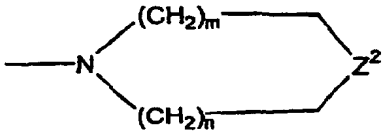
Z^1 is

(a) $-(CH_2)_p W(CH_2)_q-$;
(b) $-O(CH_2)_p CR^5R^6-$;
(c) $-O(CH_2)_pW(CH_2)_q-$;
(d) $-OCHR^2CHR^3-$; or
(e) $-SCHR^2CHR^3-$;

G is

(a) $-NR^7R^8$;

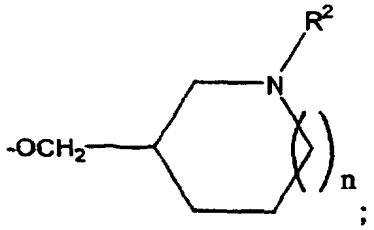
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

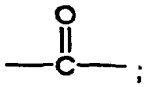
(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



W is

(a) $-CH_2-$;
(b) -CH=CH-;
(c) -O-;
(d) $-NR^2-$;
(e) $-S(O)_n-$;
(f)



(g) $-CR^2(OH)-$;
(h) $-CONR^2-$;
(i) $-NR^2CO-$;
(j)

or
(k) -C≡C-;

R is hydrogen or C_1-C_6 alkyl;
R^2 and R^3 are independently

(a) hydrogen; or
(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;
(b) halogen;
(c) C_1-C_6 alkyl;
(d) C_1-C_4 alkoxy;
(e) C_1-C_4 acyloxy;
(f) C_1-C_4 alkylthio;
(g) C_1-C_4 alkylsulfinyl;
(h) C_1-C_4 alkylsulfonyl;
(i) hydroxy (C_1-C_4)alkyl;
(j) aryl (C_1-C_4)alkyl;
(k) -CO_2H;
(l) -CN;
(m) -CONHOR;
(n) -SO_2NHR;
(o) -NH_2,
(p) C_1-C_4 alkylamino;
(q) C_1-C_4 dialkylamino;
(r) -$NHSO_2$R;
(s) -NO_2;
(t) -aryl; or
(u) -OH;

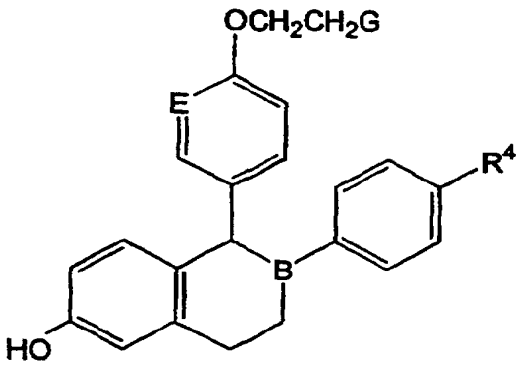
R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;
R^7 and R^8 are independently

(a) phenyl;
(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;
(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
(d) H;
(e) C_1-C_6 alkyl; or
(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;
a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
e is 0, 1 or 2;
m is 1, 2 or 3;
n is 0, 1 or 2;
p is 0, 1, 2 or 3;
q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof, or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof,
in the manufacture of a medicament for the treatment of cancer of the liver, ovarian cancer. a desmoid tumour, glioma, pancreatic cancer or renal cell carcinoma.

2. The use of claim 1 wherein the estrogen agonist / antagonist is a compound of formula (IA)



(IA)

wherein G is

;

R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or a prodrug thereof.

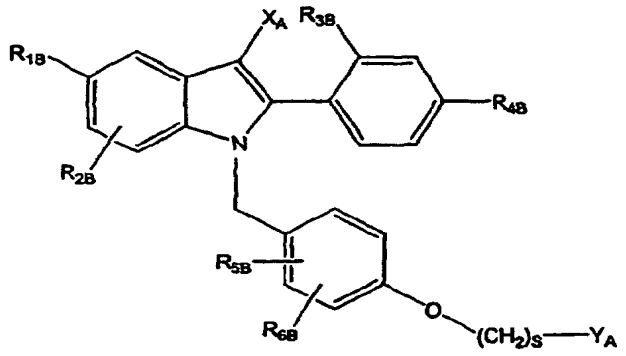
3. The use of claim 1 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

4. The use of claim 1 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

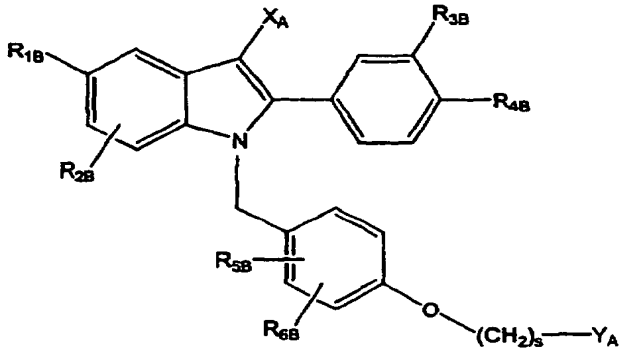
5. The use of an estrogen agonist/antagonist selected from

A) 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, raloxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1 -yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, or an optical or geometric isomer thereof; pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug thereof;

B) a compound of formula V or VI:



(V)



(VI)

wherein:

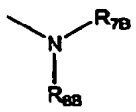
R_{1B} is selected from H, OH, -O-C(O)-C_1-C_{12} alkyl (straight chain or branched), -O-C_1-C_{12} alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH, -O-C(O)-C_1-C_{12} (straight chain or branched), -O-C_1-C_{12} (straight chain or branched or cydic), halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is the moiety:



wherein:

a) R_{7B} and R_{8B} are independently selected from the group of H, C_1-C_6 alkyl or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, $-CF_3$, or $-OCF_3$; or

b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_{1B}$, $-NH_2$, -NH(C_1-C_4 alkyl). -N(C_1-C_4 alkyl)2, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

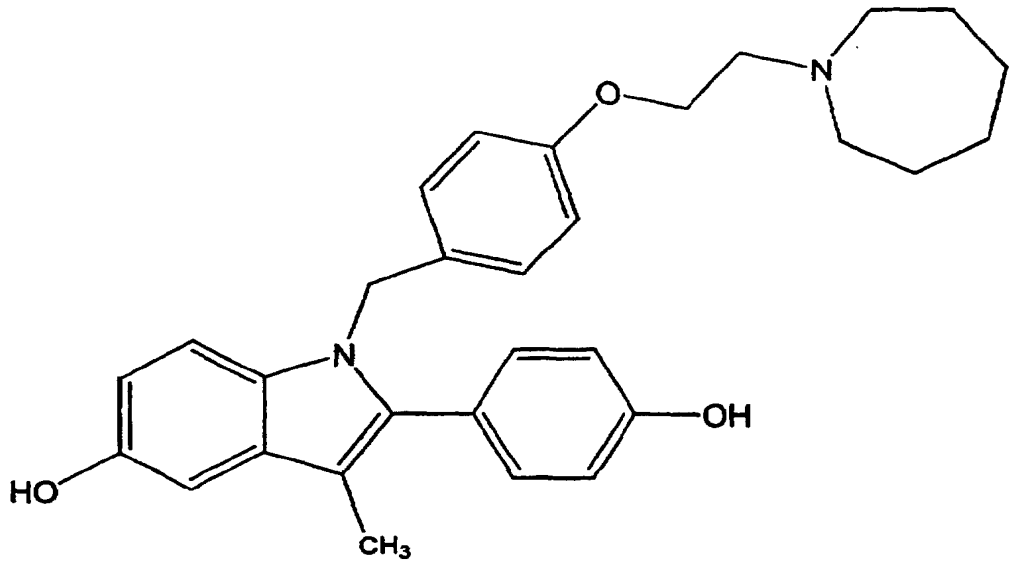
c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_{1B}$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_{1B}$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, $-NHSO_2$ R_{1B}, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocyde being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_{1B}$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-N0_2$, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom. the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2$ H, -CN, $-CONHR_{1B}$. $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof;

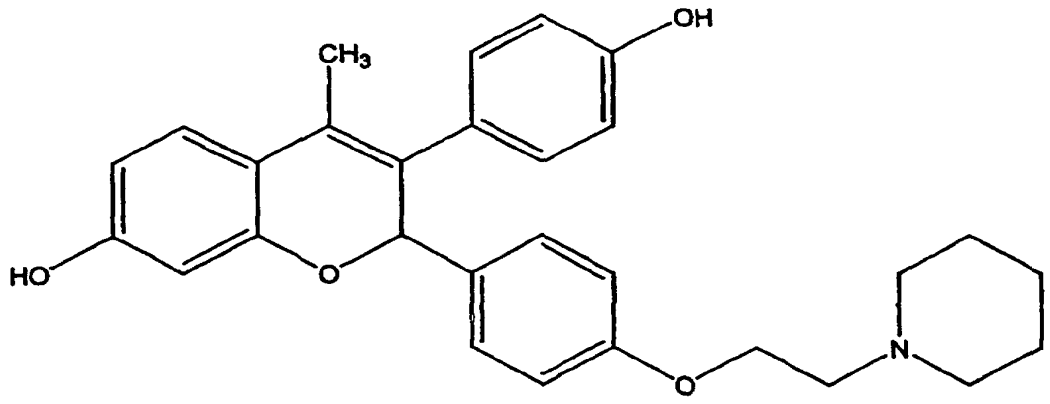
C) the compound of formula Va:



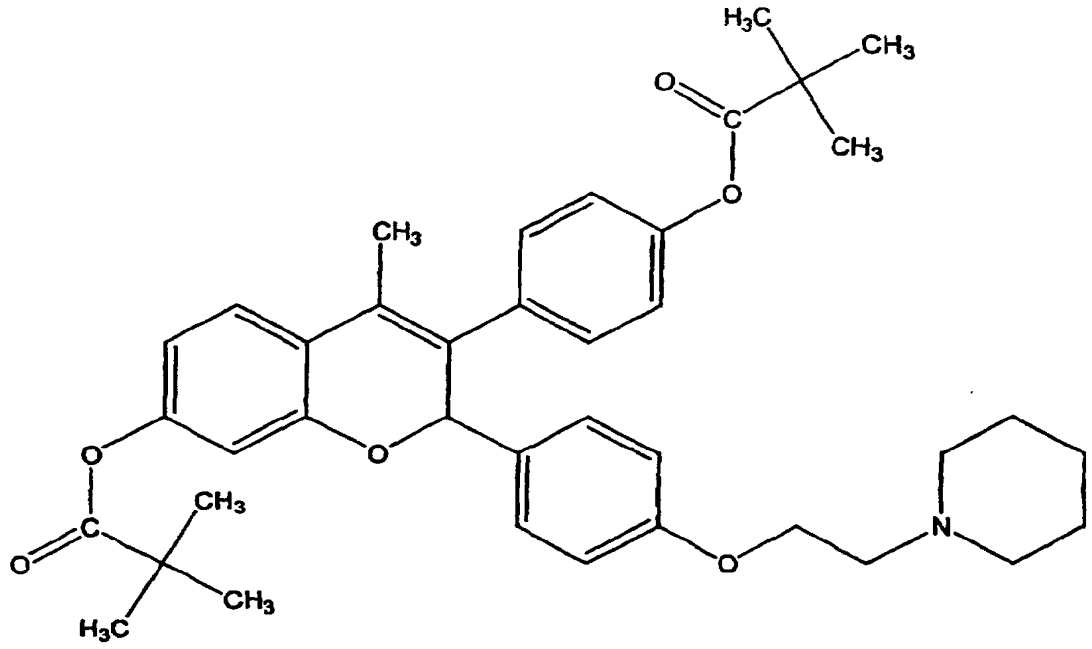
(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quatemary ammonium salt or prodrug thereof; or

D) the compound of formula III (EM-652) or formula IV (EM-800) below:



(III)

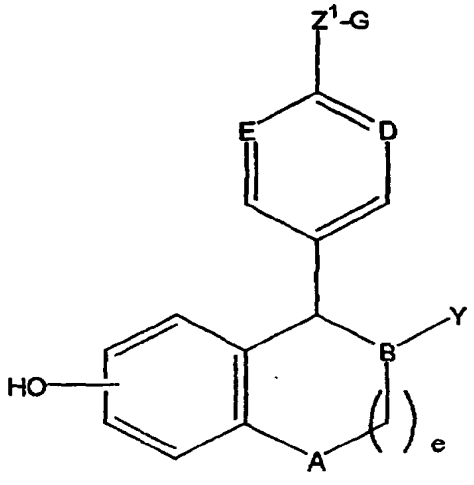


(IV)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof;
in the manufacture of a medicament for the treatment of cancer of the liver, ovarian cancer, a desmoid tumour, glioma, pancreatic cancer or renal cell carcinoma.

6. A kit for use by a consumer to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma, the kit comprising:

(a) a pharmaceutical composition comprising an estrogen agonist / antagonist that is compound of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;
B, D and E are independently selected from CH and N;
Y is

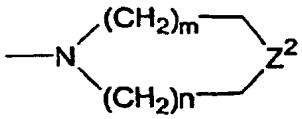
(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;
(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;
(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;
(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;
(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;
(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4; or
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

Z^1 is

(a) $-(CH_2)_pW(CH_2)_q-$;
(b) $-O(CH_2)_pCR^5R^6-$;
(c) $-O(CH_2)_pW(CH_2)_q-$,
(d) $-OCHR^2CHR^3-$; or
(e) $-SCHR^2CHR^3-$;

G is

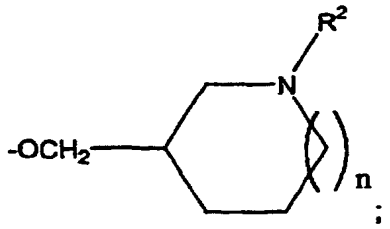
(a) $-NR^7R^8$;
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

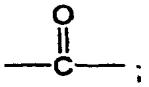
Z^1 and G in combination may be



W is

(a) $-CH_2-$;

(b) -CH=CH-;
(c) -O-;
(d) -NR^2-;
(e) -$S(O)_n$-;
(f)



;

(g) -$CR^2(OH)$-;
(h) -$CONR^2$-;
(i) -NR^2CO-;
(j)

;

or
(k) -C≡C-;

R is hydrogen or C_1-C_6 alkyl;
R^2 and R^3 are independently

(a) hydrogen; or
(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;
(b) halogen;
(c) C_1-C_6 alkyl;
(d) C_1-C_4 alkoxy;
(e) C_1-C_4 acyloxy;
(f) C_1-C_4 alkylthio;
(g) C_1-C_4 alkylsulfinyl;
(h) C_1-C_4 alkylsulfonyl;
(i) hydroxy (C_1-C_4)alkyl;
(j) aryl (C_1-C_4)alkyl;
(k) -CO_2H;
(l) -CN;
(m) -CONHOR;
(n) -SO_2NHR;
(o) -NH_2;
(p) C_1-C_4 alkylamino;
(q) C_1-C_4 dialkylamino;
(r) -$NHSO_2R$;
(s) -NO_2;
(t) -aryl; or
(u) -OH;

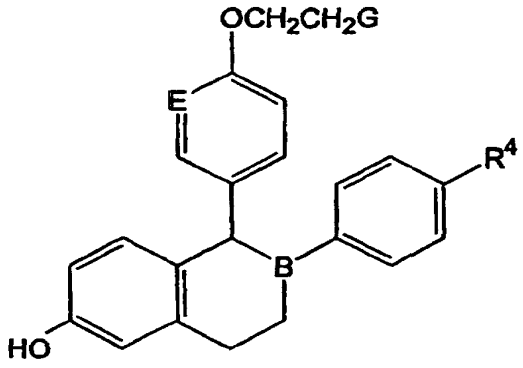
R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;
R^7 and R^8 are independently

(a) phenyl;
(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;
(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-. -N- and -S-;
(d) H;
(e) C_1-C_6 alkyl; or
(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;
a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
e is 0, 1 or 2;
m is 1, 2 or 3;
n is 0, 1 or 2;
p is 0, 1, 2 or 3;
q is 0, 1, 2 or 3;
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; and

(b) instructions describing a method of using the pharmaceutical composition to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

7. The kit of claim 6 wherein the estrogen agonist / antagonist is a compound of formula (IA):



(IA)

wherein G is

;

R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

8. The kit of claim 6 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

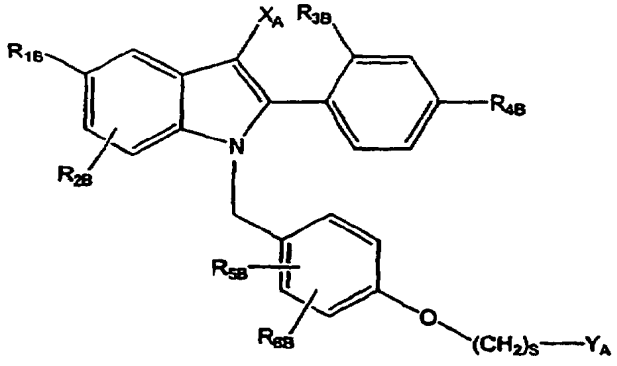
9. The kit of claim 6 wherein the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

10. A kit for use by a consumer to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma, the kit comprising:

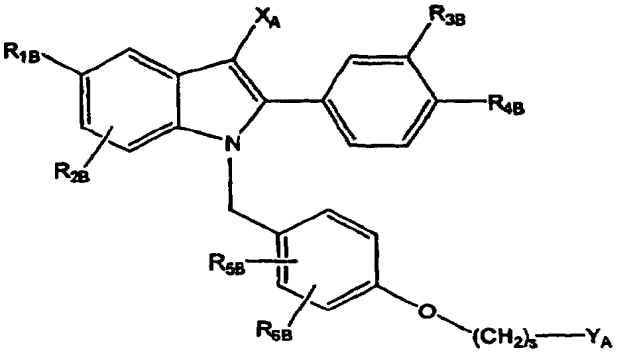
(a) a pharmaceutical composition comprising an estrogen agonist / antagonist compound selected from:

A) 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, raloxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, or an optical or geometric isomer thereof; pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug thereof;

B) a compound of formula V or VI:



(V)



(VI)

wherein:

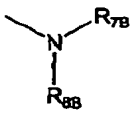
R_{1B} is selected from H, OH, -O-C(O)-C_1-C_{12} alkyl (straight chain or branched), -O-C_1-C_{12} alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH, -O-C(O)-C_1-C_{12} (straight chain or branched), -O-C_1-C_{12} (straight chain or branched or cyclic), halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is the moiety:



wherein:

a) R_{7B} and R_{8B} are independently selected from the group of H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, -CF_3, or -OCF_3; or

b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocyde containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

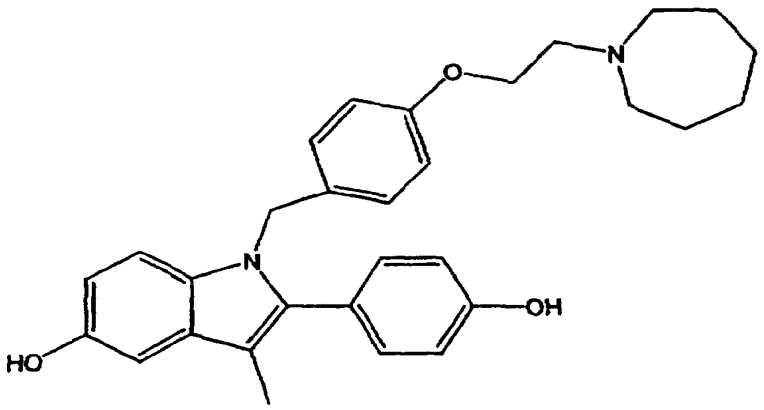
d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocyde containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -$CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom. the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2 H, -CN, - $CONHR_{1B}$, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, or phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or

prodrug thereof;

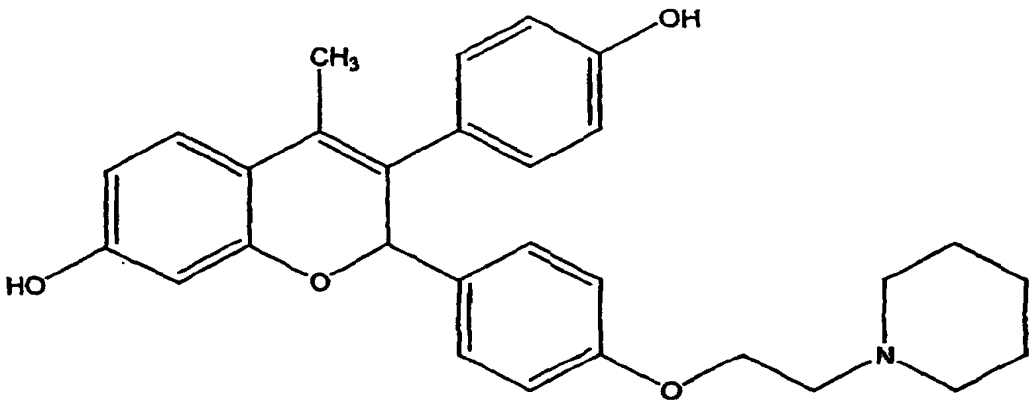
C) the compound of formula Va (TSE-424) below:



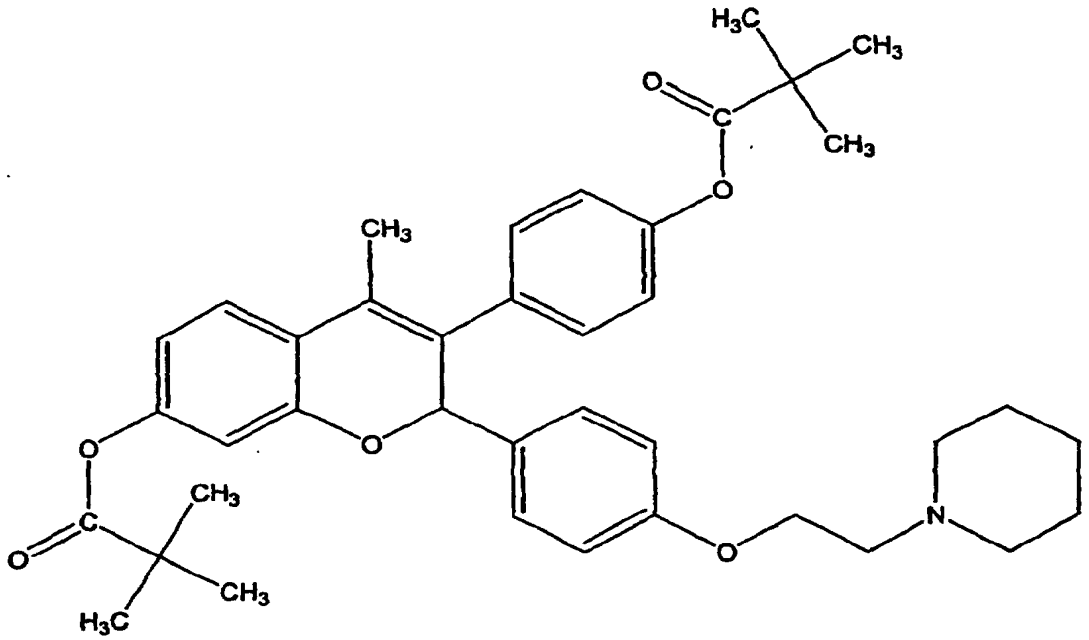
(Va)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; or

D) the compound of formula III (EM-652) or formula IV (EM-800) below:



(III)



(IV)

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; and

(b) instructions describing a method of using the pharmaceutical composition to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

11. The kit of daim 6 wherein the kit further comprises an additional compound that is useful to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

(19) Europäisches Patentamt
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(11) EP 1 226 823 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
16.04.2003 Bulletin 2003/16

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31.07.2002 Bulletin 2002/31

(21) Application number: **02250200.9**

(22) Date of filing: **11.01.2002**

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Groton, Connecticut 06340 (US)

(72) Inventor: **Rosati, Robert Louis**
Groton, Connecticut 06340 (US)

(74) Representative: **Ruddock, Keith Stephen et al**
Pfizer Limited,
UK Patent Department,
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(54) Method of treating certain cancers using an estrogen agonist/antagonist

(57) The present invention provides methods of treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma using an estrogen agonist / antagonist. The present invention also provides kits that contain an estrogen agonist /antagonist for treating cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer, or renal cell carcinoma.

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 02 25 0200

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 97 26878 A (LILLY CO ELI ;BRANDI MARIA L (IT); TONELLI FRANCESCO (IT)) 31 July 1997 (1997-07-31) * page 1, paragraph 1 - paragraph 3 * * page 2, line 25 - page 3, line 21 * * examples 2-5 * * claims 1-4 *	5,10	A61K31/404 A61K31/352 A61K31/55 A61P35/00 A61K31/40 A61K31/47 A61K31/38 A61K31/135
X	US 5 192 525 A (WALLACE SIDNEY ET AL) 9 March 1993 (1993-03-09) * column 9, line 54 - line 60 * * column 1, line 15 - line 42 *	5,10	
X	US 6 153 622 A (KE HUA ZHU ET AL) 28 November 2000 (2000-11-28) * example 1 * * claims 1,20 *	1-4,6,7,9,11	
E	EP 1 177 787 A (PFIZER PROD INC) 6 February 2002 (2002-02-06) * claim 3 * * example 2 *	1-11	

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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for those claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched

Reason for the limitation of the search

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	7 February 2003	Bonzano, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 02 25 0200

Claim(s) searched completely:
none

Claim(s) searched incompletely:
1-11

Reason for the limitation of the search:

Present claims 1,6,11 relate to an extremely large number of possible compounds (compounds corresponding to the whole formula I).
Moreover, claims 1-10 relate also to an extremely large number of possible compounds (any ester).
Support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
The term "prodrug thereof", used in claims 1-3,5-8,10 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 84 EPC).
Moreover, claim 11 relate to a compound defined by reference to a desirable characteristic or property, "additional compound that is useful to treat cancer of the liver, ovarian cancer, a desmoid tumor, glioma, pancreatic cancer or renal cell carinoma" .
The claim cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims relating to the compounds mentioned in claims 3,4, 5A-D and described in claim 2, even though the application is essentially short of support and disclosure.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 0200

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int Cl 7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P,X	EP 1 120 114 A (PFIZER PROD INC) 1 August 2001 (2001-08-01) * claims 1,6,7 *	1-11	
X	EP 1 004 306 A (PFIZER PROD INC) 31 May 2000 (2000-05-31) * claims 1-3 * * paragraph [0011] * * paragraph [0027] - paragraph [0031] *	1-11	
A	EP 0 843 999 A (PFIZER) 27 May 1998 (1998-05-27) * claims 1-3 *		
X	EP 0 702 962 A (LILLY CO ELI) 27 March 1996 (1996-03-27) * claims 1-3 * * example 2 * * page 3, line 1 - line 26 *	5,10 1,5	TECHNICAL FIELDS SEARCHED (Int.Cl 7)
P,X	EP 1 118 323 A (PFIZER PROD INC) 25 July 2001 (2001-07-25) * paragraph [0040] - paragraph [0043] * * paragraph [0063] - paragraph [0064] * * paragraph [0106]; example 2 *	6	
X	WO 97 16434 A (CHIU CHARLES K ;MELTZ MORGAN (US); PFIZER (US)) 9 May 1997 (1997-05-09) * claims 1,7 *	6	
X	US 5 552 412 A (ROSATI ROBERT L ET AL) 3 September 1996 (1996-09-03) * column 3, line 7 - line 50 * * column 7, line 7 - line 16 *	6	
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EPO FORM 1503 03.82 (P04C10)

European Patent Office

Application Number
EP 02 25 0200

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 0200

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	YANG, XIAOJING ET AL: "Enzyme-Catalyzed Asymmetric Deacylation for the Preparation of Lasofoxifene (CP 336156), a Selective Estrogen Receptor Modulator" ORGANIC LETTERS (2000), 2(25), 4025-4027, XP001097178 * page 4025, column 1, line 1 - column 2, line 6 * ---	1-4,6-9, 11	
A	ROSATI, ROBERT L. ET AL: "Discovery and Preclinical Pharmacology of a Novel, Potent, Nonsteroidal Estrogen Receptor Agonist/Antagonist, CP-336156, a Diaryltetrahydronaphthalene" JOURNAL OF MEDICINAL CHEMISTRY (1998), 41(16), 2928-2931, XP000891443 * page 1, column 2, line 26 - line 28 * * page 2930, column 2, paragraph 2 * ---		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	GELMAN: "Tamoxifen for the treatment..." SEMINARS IN ONCOLOGY, vol. 24, no. 1, 1997, pages 65-70, XP008008784 * page 65, column 2, paragraph 1 - page 67, column 1 * ---		
X	WO 98 56387 A (MORRIS DAVID LAWSON ;UNISEARCH LTD (AU)) 17 December 1998 (1998-12-17) * claims 1,10 * * page 8, line 8 - line 17 * ---	5,10	
A	US 5 844 001 A (LOS GERRIT ET AL) 1 December 1998 (1998-12-01) * column 1, line 41 - line 67 * * column 2, line 47 - line 58 * * column 3, line 52 - line 67 * ---		

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EPO FORM 1503 03.82 (P04C10)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 02 25 0200

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 5,10 (partially),2-4,7-9

   Use of compounds of formula Ia, including those specifically mentioned in claims 3-4, the 7th compound identified in claim 5 under A), for treating liver, pancreas, ovarian, renal cancer, desmoid tumor, glioma.

2. Claims: 5,10 (partially)

   Use of 4-hydroxy tamoxifen, tamoxifen, droloxifen, toremifen, idoxifen, gw5638, gw7604 for treating liver, pancreas, ovarian, renal cancer, desmoid tumor, glioma.

3. Claims: 5,10(partially)

   Use of the 8th compound identified in claim 5 under A), raloxifen for treating liver, pancreas, ovarian, renal cancer, desmoid tumor, glioma.

4. Claims: 5,10(partially)

   Use of a compound of formula V, VI, Va for treating liver, pancreas, ovarian, renal cancer, desmoid tumor, glioma.

5. Claims: 5,10 (partially)

   Use of centchroman, EM652, EM800 for treating liver, pancreas, ovarian, renal cancer, desmoid tumor, glioma.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 0200

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 558 877 A (MATLIN STEPHEN A ET AL) 24 September 1996 (1996-09-24) * example 1 * * column 2, line 18 - line 40 *	5,10	
A	WO 96 40616 A (UNIV TEXAS) 19 December 1996 (1996-12-19) * claims 16,22-25 *	5,10	
X	EP 0 729 755 A (LILLY CO ELI) 4 September 1996 (1996-09-04) * examples 2-5 * * page 3, line 38 - line 50 *	5,10	
D,X	US 4 623 660 A (RICHARDSON DORA N) 18 November 1986 (1986-11-18) * column 1; claims 1,6 *	6,10,11	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
D,X	US 4 696 949 A (TOIVOLA REIJO J ET AL) 29 September 1987 (1987-09-29) * claims 1,5,6 *	6,10,11	
X	MARTINDALE: "The extra Pharmacopoeia" 1993 , THE PHARMACEUTICAL PRESS , LONDON XP002228518 30 * page 1351, column 2, paragraph 3 * * page 477, column 2, paragraph 2 *	6,10,11	
A	WO 99 63974 A (ENDORECHERCHE INC) 16 December 1999 (1999-12-16) * page 10, paragraph 3 * * page 34, line 10 - page 35, line 2 *		

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 0200

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9726878 A	31-07-1997	AU 707675 B2	15-07-1999
		AU 2124097 A	20-08-1997
		CN 1209746 A	03-03-1999
		CZ 9802353 A3	17-02-1999
		EP 0907361 A1	14-04-1999
		JP 2000503995 T	04-04-2000
		NO 983452 A	27-07-1998
		PL 328127 A1	18-01-1999
		WO 9726878 A1	31-07-1997
		US 5670523 A	23-09-1997
US 5192525 A	09-03-1993	US 5219548 A	15-06-1993
		AT 130293 T	15-12-1995
		AU 664161 B2	09-11-1995
		AU 8868291 A	28-04-1992
		CA 2092996 A1	02-04-1992
		DE 69114719 D1	21-12-1995
		DE 69114719 T2	10-10-1996
		EP 0551434 A1	21-07-1993
		JP 6504522 T	26-05-1994
		WO 9206068 A1	16-04-1992
		US 6096874 A	01-08-2000
US 6153622 A	28-11-2000	US 5552412 A	03-09-1996
		AT 214382 T	15-03-2002
		DE 69525857 D1	18-04-2002
		DE 69525857 T2	28-11-2002
		DK 802910 T3	21-05-2002
		EP 0802910 A1	29-10-1997
		FI 972903 A	08-07-1997
		JP 2972347 B2	08-11-1999
		JP 10503215 T	24-03-1998
		US 6204286 B1	20-03-2001
		AP 592 A	05-05-1997
		AU 700982 B2	14-01-1999
		AU 4091696 A	18-07-1996
		BG 62256 B1	30-06-1999
		BG 100278 A	31-05-1996
		BR 9600079 A	27-01-1998
		CA 2209925 A1	18-07-1996
		CN 1136562 A ,B	27-11-1996
		CZ 9600055 A3	16-10-1996
		EP 1151998 A1	07-11-2001
		ES 2172579 T3	01-10-2002
		HR 960010 A1	31-12-1997
		HU 9600056 A2	28-12-1998

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The members are as contained in the European Patent Office EDP file on
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07-02-2003

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 6153622	A		WO	9621656 A1	18-07-1996
			IL	116643 A	13-08-2000
			IL	130761 A	06-12-2000
			KR	190727 B1	01-06-1999
			LV	11460 A ,B	20-08-1996
			NO	960081 A	10-07-1996
			NZ	280792 A	24-11-1997
			OA	10254 A	19-09-1997
			PL	312182 A1	22-07-1996
			PT	802910 T	31-07-2002
			RO	116275 B	29-12-2000
			RU	2130454 C1	20-05-1999
			SG	47377 A1	17-04-1998
			SI	9600004 A	31-10-1996
			SK	164895 A3	07-05-1997
			TR	960693 A2	21-08-1996
			US	2002132816 A1	19-09-2002
			US	6441193 B1	27-08-2002
			ZA	9600095 A	08-07-1997
EP 1177787	A	06-02-2002	AU	5767101 A	31-01-2002
			EP	1177787 A2	06-02-2002
			HU	0103078 A2	29-05-2002
			JP	2002087992 A	27-03-2002
			US	2002016340 A1	07-02-2002
EP 1120114	A	01-08-2001	AU	1367601 A	19-07-2001
			EP	1120114 A2	01-08-2001
			HU	0100120 A2	28-10-2002
			JP	2001213776 A	07-08-2001
			NZ	509321 A	25-10-2002
			US	2001041718 A1	15-11-2001
EP 1004306	A	31-05-2000	AU	4341099 A	02-03-2000
			EP	1004306 A2	31-05-2000
			HU	9902674 A2	28-03-2001
			JP	2000080038 A	21-03-2000
			KR	2000017101 A	25-03-2000
			ZA	9905029 A	05-02-2001
EP 0843999	A	27-05-1998	AU	735617 B2	12-07-2001
			AU	4518597 A	21-05-1998
			EP	0843999 A1	27-05-1998
			HU	9702039 A2	28-06-1999
			JP	10147522 A	02-06-1998
			NZ	329188 A	25-08-2000

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0843999	A		US	6124346 A	26-09-2000
			US	6069175 A	30-05-2000
			ZA	9710295 A	14-05-1999
EP 0702962	A	27-03-1996	US	5658931 A	19-08-1997
			AU	3643095 A	09-04-1996
			EP	0702962 A2	27-03-1996
			WO	9609052 A1	28-03-1996
EP 1118323	A	25-07-2001	AU	1113101 A	19-07-2001
			EP	1118323 A2	25-07-2001
			HU	0100119 A2	28-10-2002
			JP	2001226265 A	21-08-2001
			US	2001056099 A1	27-12-2001
WO 9716434	A	09-05-1997	AP	713 A	28-12-1998
			AU	708841 B2	12-08-1999
			AU	6998496 A	22-05-1997
			BG	102474 A	30-06-1999
			BR	9611436 A	23-03-1999
			CA	2236673 A1	09-05-1997
			CN	1201458 A ,B	09-12-1998
			CZ	9801320 A3	17-03-1999
			EG	21095 A	31-10-2000
			EP	0876359 A1	11-11-1998
			HR	960503 A1	30-04-1998
			HU	9900087 A2	28-05-1999
			WO	9716434 A1	09-05-1997
			IL	124027 A	31-10-2001
			JP	11502866 T	09-03-1999
			JP	3088020 B2	18-09-2000
			NO	981962 A	30-04-1998
			NZ	318498 A	29-06-1999
			PL	326498 A1	28-09-1998
			RU	2162465 C2	27-01-2001
			SK	54298 A3	12-07-1999
			TR	9800783 T2	21-08-1998
			US	5948809 A	07-09-1999
			ZA	9609212 A	04-05-1998
US 5552412	A	03-09-1996	AP	592 A	05-05-1997
			AT	214382 T	15-03-2002
			AU	700982 B2	14-01-1999
			AU	4091696 A	18-07-1996
			BG	62256 B1	30-06-1999
			BG	100278 A	31-05-1996

EPO FORM P3456

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 0200

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information

07-02-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5552412 A		BR 9600079 A	27-01-1998
		CA 2209925 A1	18-07-1996
		CN 1136562 A ,B	27-11-1996
		CZ 9600055 A3	16-10-1996
		DE 69525857 D1	18-04-2002
		DE 69525857 T2	28-11-2002
		DK 802910 T3	21-05-2002
		EP 1151998 A1	07-11-2001
		EP 0802910 A1	29-10-1997
		ES 2172579 T3	01-10-2002
		FI 972903 A	08-07-1997
		HR 960010 A1	31-12-1997
		HU 9600056 A2	28-12-1998
		WO 9621656 A1	18-07-1996
		IL 116643 A	13-08-2000
		IL 130761 A	06-12-2000
		JP 2972347 B2	08-11-1999
		JP 10503215 T	24-03-1998
		KR 190727 B1	01-06-1999
		LV 11460 A ,B	20-08-1996
		NO 960081 A	10-07-1996
		NZ 280792 A	24-11-1997
		OA 10254 A	19-09-1997
		PL 312182 A1	22-07-1996
		PT 802910 T	31-07-2002
		RO 116275 B	29-12-2000
		RU 2130454 C1	20-05-1999
		SG 47377 A1	17-04-1998
		SI 9600004 A	31-10-1996
		SK 164895 A3	07-05-1997
		TR 960693 A2	21-08-1996
		US 6153622 A	28-11-2000
		US 2002132816 A1	19-09-2002
		US 6441193 B1	27-08-2002
		US 6204286 B1	20-03-2001
		ZA 9600095 A	08-07-1997
WO 9856387 A	17-12-1998	AU 735676 B2	12-07-2001
		AU 7631698 A	30-12-1998
		WO 9856387 A1	17-12-1998
		CN 1261800 T	02-08-2000
		EP 1003523 A1	31-05-2000
		JP 2002504100 T	05-02-2002
		US 6486144 B1	26-11-2002
		ZA 9805028 A	25-01-1999

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 0200

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07-02-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5844001 A	01-12-1998	AU 692763 B2	18-06-1998
		AU 6273294 A	14-09-1994
		CA 2156826 A1	01-09-1994
		EP 0686038 A1	13-12-1995
		IL 108722 A	26-07-2000
		JP 8507079 T	30-07-1996
		NO 953349 A	25-08-1995
		NZ 262825 A	24-06-1997
		WO 9418990 A1	01-09-1994
		US 6288111 B1	11-09-2001
		ZA 9401290 A	25-08-1995
US 5558877 A	24-09-1996	AT 192036 T	15-05-2000
		DE 69424147 D1	31-05-2000
		DE 69424147 T2	14-12-2000
		DK 664120 T3	18-09-2000
		EP 0664120 A1	26-07-1995
		ES 2145113 T3	01-07-2000
		GR 3033571 T3	29-09-2000
		JP 7252142 A	03-10-1995
		PT 664120 T	31-08-2000
WO 9640616 A	19-12-1996	US 6096874 A	01-08-2000
		AU 6164696 A	30-12-1996
		WO 9640616 A1	19-12-1996
EP 0729755 A	04-09-1996	AU 5028696 A	18-09-1996
		CA 2214080 A1	06-09-1996
		CN 1176600 A	18-03-1998
		EP 0729755 A2	04-09-1996
		FI 973521 A	27-08-1997
		HU 9801327 A2	28-06-1999
		JP 11501033 T	26-01-1999
		NO 973963 A	28-08-1997
		WO 9626727 A1	06-09-1996
		ZA 9601564 A	27-08-1997
US 4623660 A	18-11-1986	AR 218326 A1	30-05-1980
		AT 358023 B	11-08-1980
		AT 610378 A	15-01-1980
		AU 524339 B2	09-09-1982
		AU 3900678 A	21-02-1980
		BG 30015 A3	16-03-1981
		CA 1088950 A1	04-11-1980
		CS 208659 B2	15-09-1981
		DD 138313 A5	24-10-1979

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 0200

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07-02-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4623660 A		DE 2860900 D1	05-11-1981
		DK 370778 A	23-02-1979
		EP 0002097 A1	30-05-1979
		ES 472742 A1	16-02-1979
		FI 782546 A	23-02-1979
		HU 177650 B	28-11-1981
		IE 47237 B1	25-01-1984
		IL 55387 A	30-07-1982
		IT 1098276 B	07-09-1985
		JP 54044644 A	09-04-1979
		NO 782768 A ,B,	23-02-1979
		NZ 188151 A	29-05-1981
		PT 68458 A	01-08-1978
		RO 79083 A1	25-06-1982
		SU 793382 A3	30-12-1980
		YU 199478 A1	31-10-1982
		PL 209157 A1	04-06-1979
		ZA 7804601 A	29-08-1979
US 4696949 A	29-09-1987	GB 2126576 A	28-03-1984
		AT 22064 T	15-09-1986
		AU 556608 B2	13-11-1986
		AU 1494683 A	19-01-1984
		BG 60760 B2	29-02-1996
		CA 1185977 A1	23-04-1985
		DD 230864 A1	11-12-1985
		DE 3366021 D1	16-10-1986
		DK 236583 A	28-11-1983
		EP 0095875 A2	07-12-1983
		FI 831584 A ,B,	28-11-1983
		HU 41723 A2	28-05-1987
		HU 34944 A2	28-05-1985
		IE 55023 B1	25-04-1990
		IL 68784 A	30-11-1986
		JP 1867986 C	26-08-1994
		JP 3007239 A	14-01-1991
		JP 5079654 B	04-11-1993
		JP 2105540 C	06-11-1996
		JP 6056724 A	01-03-1994
		JP 7042241 B	10-05-1995
		JP 1959197 C	10-08-1995
		JP 6078257 B	05-10-1994
		JP 6100485 A	12-04-1994
		LU 88803 A9	05-11-1996
		LV 5066 A3	10-06-1993
		NO 831873 A ,B,	28-11-1983

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 0200

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07-02-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4696949 A		NZ 204349 A	20-03-1985
		SG 65488 G	16-06-1989
		SU 1508955 A3	15-09-1989
		US 5491173 A	13-02-1996
		US 4996225 A	26-02-1991
WO 9963974 A	16-12-1999	US 6465445 B1	15-10-2002
		AU 4253099 A	30-12-1999
		BR 9911116 A	28-02-2001
		CA 2334577 A1	16-12-1999
		WO 9963974 A2	16-12-1999
		CN 1312718 T	12-09-2001
		EP 1083905 A2	21-03-2001
		HU 0103345 A2	28-02-2002
		JP 2002517433 T	18-06-2002
		NO 20006254 A	01-02-2001
		PL 345887 A1	14-01-2002
		TR 200100551 T2	23-07-2001
		TR 200103453 T2	21-06-2002
		TR 200103454 T2	21-06-2002
		TR 200103455 T2	21-06-2002
		TR 200103456 T2	21-06-2002

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No 12/82